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## Arterial Tortuosity: An imaging biomarker of childhood stroke pathogenesis?

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### Abstract

**Background and Purpose**—Arteriopathy is the leading cause of childhood arterial ischemic stroke (AIS). Mechanisms are poorly understood but may include inherent abnormalities of arterial structure. Extracranial dissection is associated with connective tissue disorders in adult stroke. Focal cerebral arteriopathy (FCA) is a common syndrome where pathophysiology is unknown but may include intracranial dissection or transient cerebral arteriopathy (TCA). We aimed to quantify cerebral arterial tortuosity in childhood AIS, hypothesizing increased tortuosity in dissection.

**Methods**—Children (1month-18 years) with AIS were recruited within the Vascular Effects of Infection in Pediatric Stroke (VIPS) study with controls from the Calgary Pediatric Stroke Program. Objective, multi-investigator review defined diagnostic categories. A validated imaging software method calculated mean arterial tortuosity of the major cerebral arteries using 3D time-of-flight MR angiography source images. Tortuosity of unaffected vessels was compared between children with dissection, TCA, meningitis, moyamoya, cardioembolic strokes and controls (ANOVA, post-hoc Tukey). Trauma-related versus spontaneous dissection was compared (Student's t-test).

**Results**—One hundred fifteen children were studied (median 6.8 years, 43% female). Age and sex were similar across groups. Tortuosity means and variances were consistent with validation studies. Tortuosity in controls ( $1.346 \pm 0.074$ ,  $n=15$ ) was comparable to moyamoya ( $1.324 \pm 0.038$ ,  $n=15$ ,  $p=0.998$ ), meningitis ( $1.348 \pm 0.052$ ,  $n=11$ ,  $p=0.989$ ) and cardioembolic ( $1.379 \pm 0.056$ ,  $n=27$ ,  $p=0.190$ ) cases. Tortuosity was higher in both extracranial dissection ( $1.404 \pm 0.084$ ,  $n=22$ ,  $p=0.021$ ) and TCA ( $1.390 \pm 0.040$ ,  $n=27$ ,  $p=0.001$ ) children. Tortuosity was not different between traumatic versus spontaneous dissection ( $p=0.70$ ).

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\* Appendix

Disclosures: None

**Conclusion**—In children with dissection and TCA cerebral arteries demonstrate increased tortuosity. Quantified arterial tortuosity may represent a clinically relevant imaging biomarker of vascular biology in pediatric stroke.

### Keywords

childhood stroke; arterial tortuosity; arteriopathy; MR angiography; dissection

### Background

Arteriopathy is the leading cause of childhood arterial ischemic stroke (AIS) and its recurrence<sup>1–3</sup>. Outcomes are poor with most survivors suffering lifelong disability. Mechanisms are poorly understood, limiting treatment and prevention strategies. The most common syndrome is a unilateral stenotic arteriopathy of the internal, middle, and anterior cerebral artery trifurcation; the term “focal cerebral arteriopathy of childhood (FCA)” has been coined to describe this imaging appearance in children. The differential diagnosis for FCA includes transient cerebral arteriopathy (TCA), a presumed inflammatory arteriopathy that can have distinct angiographic features (like arterial banding) and by definition has a monophasic natural history<sup>3</sup>. Intracranial dissection has also been suggested as a mechanism for FCA with supportive evidence including possible associations between childhood AIS and trauma, a lack of inflammatory biomarkers, and small pathological series demonstrating dissection in FCA cases<sup>4</sup>.

An improved understanding of the vascular biology underlying childhood cerebral arteriopathy is essential to develop treatment strategies and improve outcomes. Large and medium cerebral arteries are inaccessible to pathological examination, however radiographic imaging of arteriopathy is an alternative, rapidly evolving approach to assessing arterial properties *in vivo*<sup>5</sup>. A growing number of associations between childhood arteriopathies and congenital, genetic syndromes further support a role for inherent abnormalities of the cerebral arteries in childhood AIS pathogenesis<sup>6,7</sup>. Abnormal arterial structure marked by having more kinks, twists, and loops can be described as more “tortuous.” Arterial tortuosity is highly variable and known to be increased in a variety of genetic connective tissue disorders (e.g. Menke's disease, Loey's-Dietz syndrome)<sup>8</sup>. A recent adult stroke study employing standardized visual categorization of cervical arterial tortuosity found an association with extracranial dissection<sup>5</sup>. However, computer-assisted analysis of MR angiograms may afford more sensitive and objective quantifications of arterial tortuosity, and has been employed to demonstrate associations with hypertension and other adult cerebrovascular conditions<sup>9,10</sup>.

Arterial tortuosity has not been investigated in childhood AIS and may represent a window into inherent vascular structure and biology. We hypothesized that arterial tortuosity (of vessels that appear unaffected on standard vascular imaging) is increased in children with stroke due to arterial dissection compared to those with stroke due to other etiologies or control children.

## Materials and Methods

### Population

This was a sub-study of the Vascular Effects of Infection in the Pediatric Stroke (VIPS) study, the complete methodology of which is described elsewhere<sup>11</sup>. VIPS was a prospective, multicenter study of childhood AIS. Children recruited were aged 1 month through 18 years with MRI-confirmed acute AIS. VIPS collected extensive infectious histories obtained through parental interview, blood and serum samples (and CSF, when clinically obtained), and standardized brain and cerebrovascular imaging. Importantly, all imaging was reviewed and classified by both the site investigator and additional centralized, multiple, expert, blinded raters. Using standardized criteria<sup>11</sup>, each case was first classified by the central review committee into one of three mutually exclusive diagnostic categories: definite, possible or no arteriopathy. Those with arteriopathy were then further classified as having secondary diagnoses including arterial dissection (spontaneous and traumatic), TCA, moyamoya, and secondary vasculitis (including meningitis). The level of certainty regarding the secondary diagnosis was also assigned. Cases with no arteriopathy were further classified as cardioembolic, other known etiology, or idiopathic. For this sub-study, we included only those subjects with the highest level of certainty regarding their diagnostic category: those classified as “definite arteriopathy” and with a secondary diagnosis classified with “high certainty,” as well as a subgroup of children with “no arteriopathy” and cardioembolic stroke. The original, anonymized DICOM files of all eligible subjects were obtained directly from the central VIPS imaging repository for analysis.

### Controls

To determine normative values for childhood craniocervical arterial tortuosity, MRA studies completed on children from the same age range were obtained from the Alberta Children's Hospital Pediatric Neuroimaging Database in accordance with previously approved methods. Criteria were (1) age 29 days to 18 years, (2) cerebral time-of-flight MRA completed between 2005-2013 (same scanner and protocol requirements as VIPS sites) and reported as normal, and (3) no history of stroke, cerebral or systemic arterial or connective tissue disease, or recent trauma. All control scans were completed on a 1.5T Siemens Avanto MRI scanner (Siemens Medical Systems, Erlangen, Germany). Both the VIPS study and this sub-study were approved by the institutional Research Ethics Board.

### Arterial tortuosity quantification

We employed a previously validated methodology using *ImageJ* software to analyze and quantify arterial tortuosity<sup>12</sup>. Our technique was similar to that previously described with slight modifications as follows. First, each subject's cerebral arteries were isolated from their 3D time-of-flight MR angiography source images in DICOM format. The imaging study of top quality closest to stroke diagnosis was used. Segments with focal disease (e.g. TCA, dissection) were not included. The algorithm iterates through each 2-dimensional source image slice in the 3-dimensional space and calculates the center of mass point (single voxel) for each cross-section of an arterial lumen and crops the rest of the local area. These center points are connected to form centerlines that make up an isolated skeleton structure of the arteries. Local and global arterial structure is maintained including bifurcations (Figure 1).

Tortuosity was then calculated for each individual artery by dividing the path length by the Euclidean (shortest) distance between its endpoints; this value is referred to as the Distance Factor Metric (DFM). The software does not distinguish arteries from one another so each arterial segment was manually defined by selecting two endpoints. A limitation in previous studies was analyzing the internal carotid and vertebral arteries as they descend down the neck lacking clearly definable endpoints. Selection of the endpoint to define the artery of interest may bias the DFM calculation (Figure 1). To address this, our methodology is designed to only require one definite endpoint such as the convergence of the vertebral arteries or bifurcation point of the internal carotid artery (ICA) at the Circle of Willis<sup>12</sup>. The second endpoint must still be placed in roughly the same area for comparable results but the margin for error is much greater. The software then iterates through each voxel along the centerline. At each voxel, the path length and Euclidian distance are calculated between it and the first endpoint generating a local DFM. After iterating through all the voxels in 3 dimensions, the final tortuosity score assigned to an artery is the maximum DFM (mDFM) generated. This choice of using mDFM was made based on previously validated methods<sup>12</sup>.

This process was repeated for each of the following major cerebral arteries: basilar, left and right vertebral, left and right internal carotids, and the M1 segments of the left and right middle cerebral arteries. Anterior cerebral and further order branches were beyond the resolution of the method. The most caudal slices available were used, resulting in vertebral and ICA imaging to the mid-cervical level. In subjects with diagnosed arteriopathy, the affected arterial segments were not included in the tortuosity measurements. Primary outcome was the tortuosity score, calculated as the mean mDFM of the seven arteries in each subject.

### Analysis and Sample size

Following confirmation of a normal distribution, the relative tortuosity of each major artery was compared using ANOVA with post-hoc Tukey test. A paired t-test compared relative symmetry between left and right for all paired vessels within subjects. Differences in mean tortuosity across control and disease groups were compared using ANOVA (post-hoc Tukey). Tortuosity of traumatic versus atraumatic dissection cases were compared with a student t-test (means) and Levene's test (variance). A blinded intra-rater analysis prior to study initiation confirmed highly reproducible mean and segmental tortuosity measurements (all intraclass correlations >0.96). Based on typical means and variances from previous adult data using similar measures<sup>12</sup>, a significant increase of 1SD in dissection subjects, and  $\alpha = 0.05$ , our sample of convenience from the VIPS study was 94% powered to address the primary hypothesis.

### Results

Of the 480 subjects enrolled in VIPS, 100 (21%) satisfied inclusion criteria for this substudy. Excluded case demographics did not differ from the study sample. The characteristics of the study population (including 15 controls) divided by group are summarized in Table 1. Age and sex were comparable across groups.

Representative examples across the spectrum of tortuosity observed are shown in Figure 2. Differences in tortuosity were not readily apparent on visual inspection of the original MRA images<sup>9</sup>. Tortuosity scores were normally distributed in all groups. Controls (93% imaged for headaches) demonstrated an average tortuosity score of 1.333 (median 1.331) with a range of 1.283 to 1.443. Average values, ranges, and variance appeared comparable to previously published values in adults<sup>9</sup>.

Across all subjects, average tortuosity varied amongst the different arterial segments ( $p<0.0001$ ) (Figure 3). Consistent with expected anatomical differences, the internal carotid had the highest values while basilar scores were lower. Tortuosity scores were symmetrical with comparable values between left and right measures of paired arteries. Tortuosity scores were not associated with age or sex (Figure 4).

Differences in mean tortuosity were observed across disease groups ( $p<0.001$ , Figure 5). Variability around this number was low with a standard deviation of 0.039. Based on control measures, the 5<sup>th</sup> and 95<sup>th</sup> percentiles for tortuosity were 1.28 to 1.44. Variance of tortuosity was also greater in dissection ( $p=0.017$ ) and TCA ( $p=0.042$ ) groups compared to controls but not compared to the other disease groups.

Compared to controls, tortuosity was higher in both dissection ( $1.398\pm0.072$ ,  $p=0.021$ ) and TCA ( $1.421\pm0.076$ ,  $p=0.001$ ) groups. Tortuosity scores were not different from controls for the remaining stroke disease groups: moyamoya ( $1.324\pm0.038$ ,  $p=0.998$ ), meningitis ( $1.348\pm0.052$ ,  $p=0.989$ ) and cardioembolic ( $1.379\pm0.056$ ,  $p=0.190$ ). Within the dissection group, mean tortuosity between traumatic ( $1.391\pm0.036$ ) and spontaneous ( $1.403\pm0.090$ ,  $p=0.671$ ) were not different although variance was higher in the spontaneous group ( $p=0.018$ ).

## Discussion

Our findings suggest that arterial tortuosity is different in children with certain forms of arteriopathic stroke, specifically dissection and TCA. Tortuosity appears to be accurately measurable from clinically obtained MRA in children. Arterial tortuosity may represent an imaging biomarker of inherent vascular biology with implications for understanding the pathophysiology of childhood stroke.

Inherent arterial structure plays a role in specific cerebrovascular diseases at all ages. The number of genetic connective tissue diseases responsible for cerebral arteriopathies continues to grow such as collagen 4A1 and A2, MOPD2, ADA2, etc<sup>13,6,14</sup>. That many of these begin early in life and are accompanied by complications throughout the arterial tree and other organs attests to the importance of inherent arterial stability in long-term health. In adult stroke due to dissection, evidence of connective tissue alterations is well established including a large proportion of otherwise asymptomatic patients with evidence of disordered collagen, elastin or other connective tissue elements visible on skin electron microscopy<sup>15,16</sup>. A recent adult stroke study described an association between visually classified tortuosity and dissection<sup>5</sup>. Linking these pathological and genetic findings with

such readily recognizable imaging biomarkers such as arterial tortuosity could facilitate the earlier assignment of likely mechanism and appropriate management in children with stroke.

The TCA syndrome is a well-established imaging syndrome but its pathophysiology has emerged as one of the most perplexing and controversial issues in childhood stroke<sup>17</sup>. Its clinical radiographic characteristics are often indistinguishable from other forms of FCA although we employed the best available consensus imaging criteria for classification. Observations of limited, weak epidemiological associations with remote infections and lack of laboratory or imaging biomarkers of inflammation have reasonably questioned the grounds for a primary infectious or inflammatory mechanism. Our finding that the mean tortuosity is different in children with TCA brings a fundamental new consideration to trying to understanding the biological mechanisms of the disease. That the inherent structural properties of the cerebral arteries should predispose one specific section to an acquired infectious or inflammatory process seems unlikely.

Could TCA be mainly due to intracranial dissection? Despite much interest and reasonable theory for an inflammatory, possibly parainfectious mechanism to TCA, definitive proof has been lacking. Transient, abnormal serum biomarkers of disordered inflammation have been described in a small case series of children with TCA as compared to those with cardioembolic stroke<sup>18</sup>. Another small case series described three children with clinically diagnosed TCA/FCA who died and went to autopsy where pathological evidence of intracranial dissection (and no evidence of inflammation) were described<sup>4</sup>. It should also be noted that these two possibilities are also not mutually exclusive (e.g. an artery damaged by acute inflammation might well be vulnerable to dissection). Our findings that TCA and dissection share a similar degree of increased tortuosity at regional / distant sites to the pathology that differentiates them from both controls and other childhood AIS subtypes does not prove that TCA is intracranial dissections. It does raise serious consideration that the inherent structure of the artery itself may be a key component of the mechanism that underlies the disease.

Our technique provides a straightforward method of objectively quantifying abnormality in arterial structure. However, several methodological issues are identified. Because this was a multi-center study where different MR scanners were used, not all imaging was standardized. Some imaging data from sites was unusable or incompatible with the software. The software method might also be improved when calculating the centerline for an artery. The 3D time-of-flight MRA source images still contained voxel information from the skull which, in some cases, added noise possibly interfering with the centerline calculations. Signal from the anterior cerebral arteries imaging were too weak to be analyzed. Increasing computational power available and improvements in the algorithm may increase our ability to capture smaller vascular structures. In our study, tortuosity scores were assigned by averaging the tortuosity score of each major artery. However it is possible that specific arteriopathies affect specific arteries differently.



## Conclusion

Arterial tortuosity is measureable in children with stroke and may represent a clinically relevant imaging biomarker of vascular biology in pediatric stroke. Children with dissection have increased arterial tortuosity and no difference was found in traumatic and spontaneous dissection. Whether this reflects inherent abnormalities of arterial structure requires further study. Children with the TCA syndrome also appear to have higher tortuosity. This provides indirect support of previous suggestions that some TCA cases are intracranial dissections.

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## APPENDIX: VIPS Investigators

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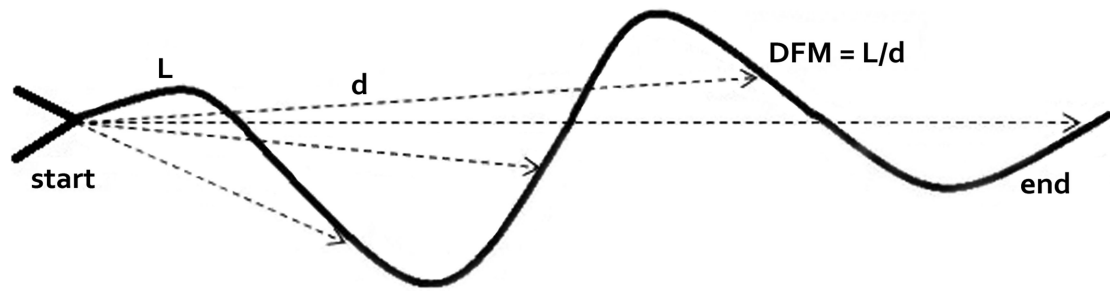
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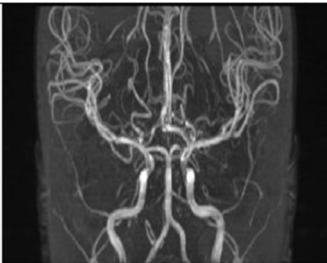


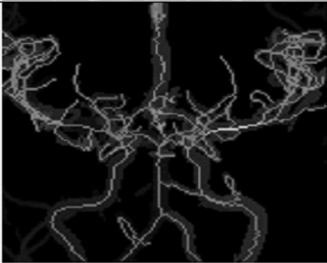

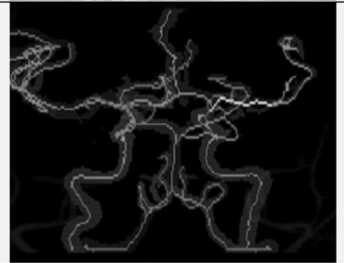
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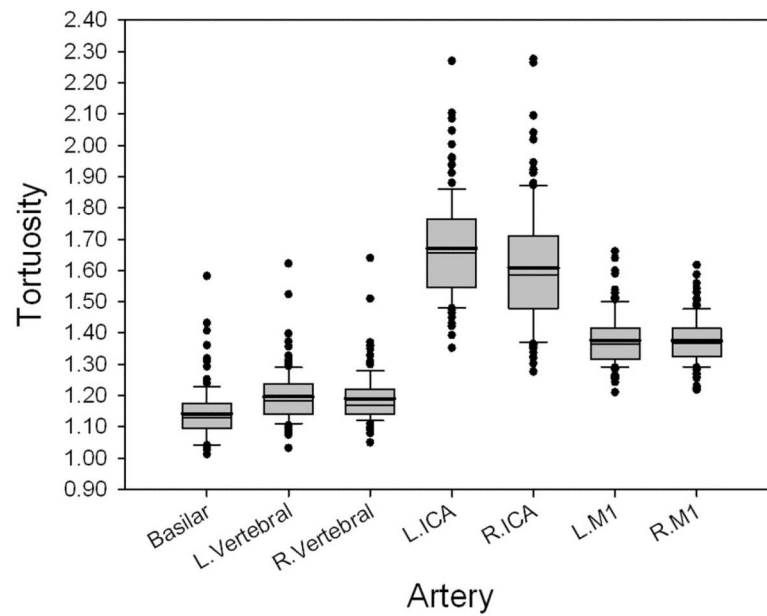
**Figure 1.**

Tortuosity Measurement. The distance factor metric was calculated to quantify relative tortuosity. Dashed arrows represent Euclidian distances ( $d$ ) to local points along artery path length ( $L$ ). Distance Factor Metric ( $DFM$ ) =  $L/d$ . Using a bifurcation point as the definite start, an iteration is performed through every voxel along path calculating a local DFM until the endpoint is reached.

MIP of TOF MRA Coronal View			
Reconstructed Skeleton Coronal View			
Average mDFM	1.237	1.460	1.608

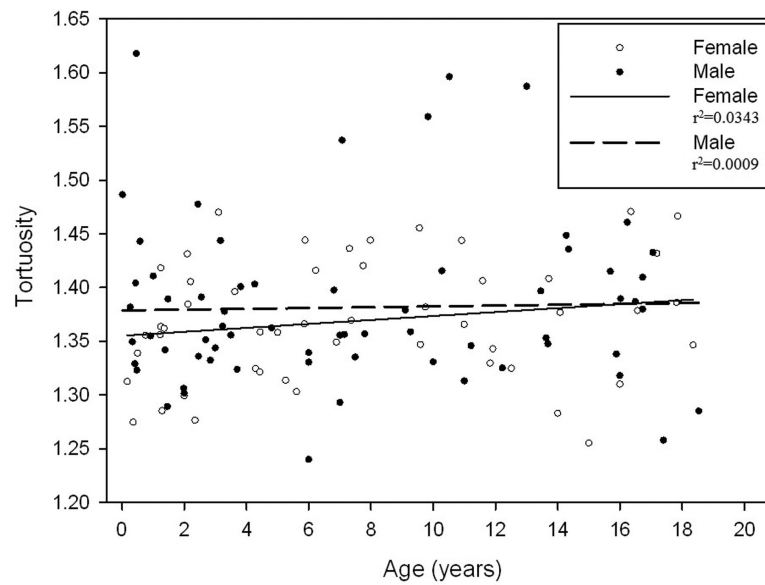
**Figure 2.**

MRA tortuosity measures. Representative examples from across the range of tortuosities calculated are demonstrated. Original clinical maximum intensity projection (MIP) of time-of-flight (TOF) MR angiogram (MRA) images (top row) and their corresponding reconstructed centerline skeletons (bottom row) depict the bottom (1.237), mean (1.460) and top (1.608) range tortuosity scores.



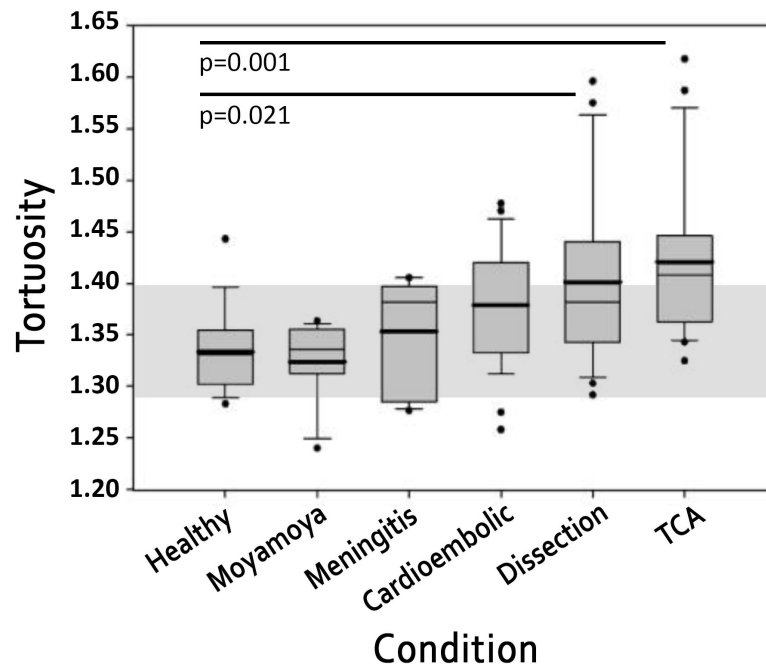
**Figure 3.**

Arterial tortuosity by location. Box plots for tortuosity scores across the entire sample are demonstrated for each major artery measured. Tortuosity was symmetrical for paired arteries, greatest in the internal carotids, and lowest in the basilar artery. ICA, internal carotid artery; M1, first segment of middle cerebral artery; L, left; R, right.



**Figure 4.**

Effects of age and gender on arterial tortuosity. A scatter plot depicts mean tortuosity scores for all subjects across the full age range with separation of male and female subjects. No association was demonstrated with age or sex.



**Figure 5.**

Tortuosity by disease. The normal range of arterial tortuosity in children is depicted by the controls (left box plot,  $n=15$ ) with the 5<sup>th</sup> and 95<sup>th</sup> percentiles marked with the shaded box. Dissection ( $n=22$ ) and TCA ( $n=25$ ) groups demonstrated abnormally elevated tortuosity and increased variance of tortuosity scores. No difference was found between traumatic ( $n=9$ ) and spontaneous ( $n=13$ ) dissection.



**Table 1**

Demographic characteristics of subjects. Typically developing controls were comparable to all childhood AIS disease groups except average age was lower in the meningitis group.

Group	N	Sex (M:F)	Age (mean $\pm$ SD) (years)
Control	15	10:5	6.25 $\pm$ 5.90
Dissection	22	13:9	9.51 $\pm$ 6.27
Moyamoya	15	8:7	6.12 $\pm$ 4.46
Meningitis	11	7:4	3.83 $\pm$ 5.22
TCA *	25	11:14	9.67 $\pm$ 4.42
Cardioembolic	27	16:11	7.38 $\pm$ 6.28

\* TCA, transient cerebral arteriopathy